Designing Microplate Layouts Using Artificial Intelligence

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Introduction

Microplates (flat plates with multiple 'wells' used as small test tubes) are indispensable in large-scale biomedical experiments

Experiments carried out using microplates commonly exhibit plate effects, which are systematic variations across the geometry of a microplate due to factors such as well location, temperature and humidity being unequally distributed, and can affect the results to the point of rendering the experiment unusable (see Figure 1).

Plate layouts are important when trying to mitigate plate effects and gaining the most of out of using control samples and error correction methods.

Common types of layouts are border, that is, placing controls in the outer-most wells, and random (see Figure 2).

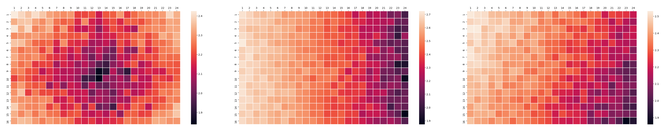

Figure 1: Examples of common plate effects. Bowl-shaped (left), linear relationship to column number (center), and linear relationship to row and column number (right).

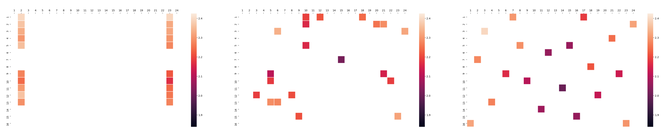

Figure 2: Examples of the distribution of negative controls in plate layouts with 20 negative controls. Border layout (left), random (center), and effective (right).

Effective Plate Layouts

We want "random-looking" layouts that can be used to effectively detect and correct errors. Some good properties include:

- Balanced number of controls between:
  - left and right halves
  - upper and lower halves
  - quadrants
  - rows
  - columns
- Keeping controls of the same type "apart"
- Compound replicas placed in different rows and columns
- Different doses of the same compound placed in different rows and columns
- . . .

We have used constraint programming (artificial intelligence) to express those properties (and more) in a high-level language so we can generate effective layouts for various kinds of experiments.

Results

More Accurate IC_{50} Estimations

Effective layouts lead to smaller errors in dose response experiments when estimating absolute and relative IC50, for varying amounts of negative controls, number of doses, replicates, as well as type and intensity of plate effects.

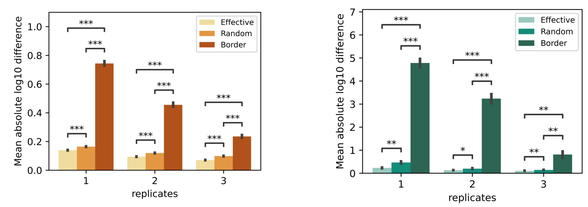

Figure 3: Mean absolute log10 difference between expected and obtained values of absolute IC_{50} (left) and relative IC_{50} (right) for dose response experiments with 8 doses, 20 negative control, and strong plate effects with a linear relationship to column number in half of the plate.

Improved Sensitivity in Screenings

Effective layouts improve sensitivity in screening experiments for varying amounts of controls and intensity of plate effects.

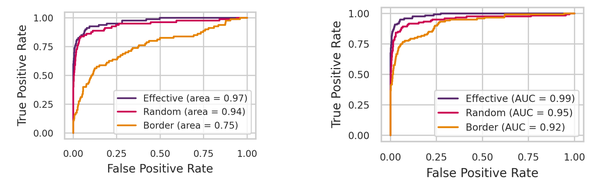

Figure 4: ROC curves obtained from simulated screening experiments using layouts with 10 negative controls and 10 positive controls in the presence of strong bowl-shaped plate effects with 0.5% hit rate (left) and 1% hit rate (right)

Conclusions

We generated effective layouts using constraint programming, that reduce unwanted bias and limits the impact of plate effects after error correction and normalization, leading to more accurate and reliable experimental results.

The impact of using effective layouts is, in general, greater than what is obtained by increasing the number of replicates or doses, making it possible to obtain better results at a lower cost.

The PLAID Online Tool

An interactive web interface that allows for specifying experimental details and generate layouts using the web browser. The experimental design can be saved in a .JSON file that can be later uploaded into the website in order to create more plate designs for the same experiment or as a base for new experiments.

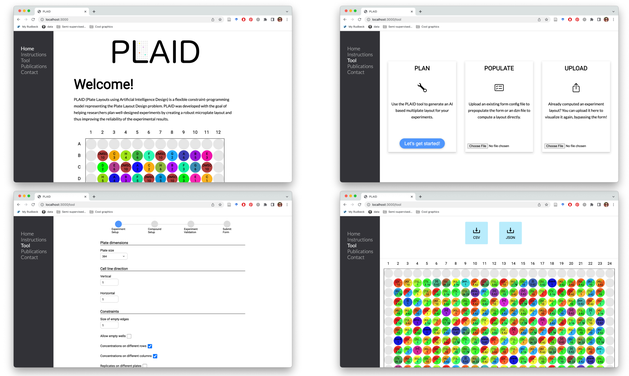

Figure 5: Screenshots of the PLAID online plate design tool.

The PLAID Ecosystem

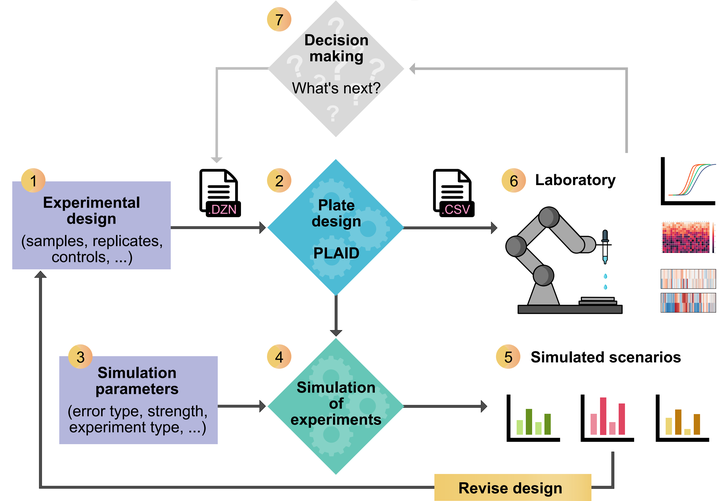

Figure 6: Overview of the PLAID ecosystem. Experimental design (1) comprises the selection of samples, replicates, concentrations, etc, and then the PLAID constraint model is called to generate the layouts (2). In order to evaluate the design, simulation parameters such as errors need to be defined (3) and then a simulated experiment using the layouts can be carried out in the PLAID Analysis and Visualization Notebooks (4). When an acceptable experiment design has been generated, the layouts can be used to drive liquid handling instruments, such as automated pipette robots (6). After the experiment is performed and analyzed, a decision can be made on subsequent experiments e.g. confirm findings, re-run failed samples, evaluate more concentrations, etc. (7). Implementing automated decision making that defines the next experiment enables autonomous sequential experimentation.

Pre-print!

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